known, and that the specification as filed does not disclose or provide evidence that points to a property of the claimed secreted protein such that another non-asserted utility would be well established. The Examiner continues by stating that, since the function of the protein is not known, the protein lacks a well established utility.

Applicants respectfully traverse these rejections based on the following remarks.

Contrary to the Examiner's assertions, the claimed isolated nucleic acid molecules, such as SEQ ID NOS:1 and 3, that encode a specified amino acid sequence, SEQ ID NO:2, and methods of using such nucleic acid molecules have several uses that meet the requirements of 35 U.S.C.§101 and the first paragraph of 35 U.S.C.§112. These, as well as the accepted state of the art view that such molecules have uses within the commercial marketplace in the drug development cycle, since they encode previously unidentified members of important pharmaceutical targets, establishes the utility of the claimed invention.

The utility requirement of a claimed invention requires that an invention must have a specific, substantial and credible utility. These requirements are defined in broad terms in cases such as *Brenner v. Manson*, 148 USPQ 689 (S. Ct. 1966) and the Utility Guidelines from the USPTO.

However, the notion that a recognized valuable addition to even entry points of the drug discovery cycle advances the art sufficient to establish a "usefulness" of a claimed invention should not be ignored. This is supported by previous case law (e.g., *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980)). Accordingly, the present invention, which is drawn to isolated nucleic acid molecules that encode a novel secreted protein (SEQ ID NO:2) that is similar to retinoic acid receptor responder secreted proteins, has valuable commercial utilities in the drug discovery process by providing previously unidentified members of an important pharmaceutical target class. The present invention provides sufficient knowledge and information that is beneficial to the public, and provides sufficient guidance for researchers to use the claimed subject matter to develop disease treatments and/or diagnostics. It is well recognized that secreted proteins are among the most important target for drug action (see, e.g., pages 1-12 of the specification). The public disclosure of a new member of the secreted protein family through the patenting process clearly advances the art and augments the capabilities of biomedical researchers to combat illnesses.

The utility rejection raised by the Examiner also conflicts with the case *Juicy Whip v. Orange Bang* (Fed. Cir. 1999). *Juicy Whip* held that, in order to violate the utility requirement, an invention must be "totally incapable of achieving a useful result." The polypeptides and encoding nucleic acid molecules of the present invention are well known in the art to be valuable drug targets and therefore have readily apparent commercial utilities, such as for screening potential drug compounds, producing antibodies, developing hybridization probes and primers, etc. Therefore, the present invention is not "totally incapable of achieving a useful result." Instead, it is useful.

Contrary to the Examiner's assertion that the claims are drawn to a polynucleotide encoding a secreted protein which is an orphan polypeptide whose function is not known, Applicants have provided sufficient guidance and functional information such that undue experimentation would not be required by one of ordinary skill in the art to know how to use the claimed invention. For example, Applicants have characterized the secreted protein of SEQ ID NO:2 as being related to retinoic acid receptor responder secreted proteins (see, e.g., lines 7-8 on page 1 of the specification), thereby further enabling one of ordinary skill in the art to use the claimed invention. Given the guidance provided in the specification and figures in combination with the knowledge in the art regarding the known biological roles of secreted proteins, particular those that are similar to retinoic acid receptor responder secreted protcins, one of ordinary skill in the art would know how to use the novel secreted proteins, and encoding nucleic acid molecules, provided by Applicants without undue experimentation.

For example, the function of retinoic acids (RAs)/retinoids, retinoic acid receptors (RARs), and retinoid X receptors (RXRs) is well known in the art and is specifically described on pages 3-12 of the specification. As indicated on line 27 of page 3 through line 18 of page 4, retinoids are essential for normal growth, vision, tissue homeostasis, reproduction and overall survival. Retinoids have been shown to be vital to the maintenance of skin homeostasis and barrier function in mammals. Retinoids are also apparently crucial during embryogenesis, since offspring of dams with vitamin A deficiency (VAD) exhibit a number of developmental defects. Most of the effects generated by VAD in animals and their fetuses can be prevented and/or reversed by retinoic acid (RA) administration. The dramatic teratogenic effects of maternal RA administration on mammalian embryos, and the marked effects of topical administration of

retinoids on embryonic development of vertebrates and limb regeneration in amphibians, have contributed to the notion that RA may have critical roles in morphogenesis and organogenesis.

Furthermore, as indicated on lines 12-29 on page 5 of the specification, RARs are the critical factors in tissue differentiation and development. They are up-regulated in rapidly dividing cells and tumors. RARs play an important role in lymphocyte activation. Synthetic antagonists of retinoic acid receptors can inhibit delayed type hypersensitivity (DTH). Growth factors and carotene regulate RXR expression levels. For example, granulocyte macrophage colony-stimulating factor induces retinoic acid receptors in myeloid leukemia cells. RARs can form heterodimers with other nuclear receptors. The protein provided by the present invention can be used as a probe to detect possible interactions in the two-hybrid assay. Synthetic peptides that mimic dimerization surface can disrupt intermolecular interactions between these receptors. RAR gene rearrangements are the primary causes of some types of leukemia and provide a convenient genetic marker for malignant cell lines. A number of retinoic acid derivatives are used in treatment of myelodysplastic disorders. They are designed to bind and activate RXRs. Beta-carotene can prevent skin tumor formation in mouse models. N-(4-hydroxyphenyl) retinamide can delay onset of dysplasia in bronchi. Different chemopreventive drugs can be designed to target individual retinoic receptors. The sequences provided by the present invention may be used to design high affinity chemopreventive compounds.

Such functions are quite specific for retinoic acids and retinoic acid receptors and enables retinoic acid receptor responder secreted proteins to be differentiated from other proteins, including other secreted proteins. As such, these functions are clearly specific enough to define uses for novel secreted proteins having similarity to retinoic acid receptor responder secreted proteins, and encoding nucleic acid molecules, in the drug discovery process, and to enable one of ordinary skill in the art to use the claimed invention without undue experimentation.

For example, because of the essential roles that retinoic acids and retinoic acid receptors play in a wide variety of important physiological processes, such as growth and development, vision, tissue homeostasis, reproduction, overall survival, and tumorigenesis, it is clear that the disclosure of novel secreted proteins having similarity to retinoic acid receptor responder secreted proteins satisfies a need in the art by providing important new compositions that are useful towards the prevention, diagnosis, and treatment of such disorders as, for example, cancer, developmental and reproductive disorders, and various tissue disorders. Consequently, one of

ordinary skill in the art would recognize that novel secreted proteins having similarity to retinoic acid receptor responder secreted proteins, and encoding nucleic acid molecules, have "real world" uses that meet the requirements of 35 U.S.C.§101.

Thus, there is overwhelming evidence in the art to support the utility of novel secreted proteins and encoding nucleic acid molecules. Not all nucleic acid molecules, and actually a very limited number, of the approximately 3 billion bases that make up the human genome will encode a protein for these and the other disclosed uses. These uses are quite specific for secreted proteins, and each is a specific composition of matter having substantial, specific and credible uses that the vast majority of other isolated nucleic acid molecules do not possess.

By placing a new secreted protein into the public domain through the patenting process, the present invention is not only a clear advancement over the prior art (a newly discovered protein/gene) but also enables significant advancement in medicine and further discovery. The Utility requirement cannot be used to contradict the reasons for the patent system, i.e., to encourage early disclosures of inventions so that others can benefit from, improve upon, and further develop such inventions. This is particularly important in medicine, wherein early disclosure of key inventions (such as new secreted proteins and encoding nucleic acid molecules) is needed to facilitate the early development of new therapies and diagnostics to treat illnesses.

The grant of a patent to the claimed isolated nucleic acid molecule and the resultant disclosure of the nucleic acid and protein sequences to the public will certainly shorten the process for medical researchers to discover other novel uses for the claimed secreted protein-encoding nucleic acids. One example disclosed in the specification is that the claimed nucleic acid molecules can be used to produce protein targets for identifying agents that bind to the protein targets and modulate protein function. Such agents that bind to a protein target and modulate cellular processes such as signal transduction may subsequently be developed and refined for use in mammalian therapeutic applications. All of this later discovery and refinement will be done using the presently claimed material. These uses are clearly commercial and substantial uses that are specific for a very limited number of proteins/nucleic acid molecules.

In addition to serving as targets for developing molecular probes and therapeutic agents, the disclosed uses of the claimed nucleic acid molecules as probes, primers, and chemical intermediates, particularly in biological assays, is sufficient to satisfy the requirements of 35 USC §101 and §112. The claimed invention is directed to nucleic acid sequences, such as SEQ ID

NOS:1 and 3, that encode a secreted protein with a specified amino acid sequence (SEQ ID NO:2). Exemplary uses of the nucleic acid sequences are clearly recited in the specification on, for example, pages 39-56. Among the examples, the nucleic acid molecules are useful as hybridization probes for messenger RNA molecules, transcript/cDNA molecules, genomic DNA, and variants thereof. An expression vector comprising the nucleic acid sequences can be constructed that expresses the secreted protein. Such uses are specific for the claimed nucleic acid molecules, and the products of such uses will be clearly different (and hence specific for the claimed molecules) than what would be produced using a different nucleic acid molecule for the same purpose.

In view of law and fact, the utility standard interpreted by the USPTO guidelines is too high. The commercial value of previously unidentified members of the secreted protein family, members of which are well known in the art to be commercially valuable drug targets, should be sufficient to satisfy the utility requirement. Therefore, applicants respectfully request that the Examiner withdraw the rejections.

Conclusions

Claims 4, 8-9, and 24-29 remain pending.

In view of the above remarks, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the rejections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent at (240) 453-3812 should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,
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